NATIONAL ACADEMIES Sciences Engineering Medicine

Forum on NEUROSCIENCE and NERVOUS SYSTEM DISORDERS

Multimodal Biomarkers for Central Nervous System Disorders: Development, Integration, and Clinical Utility

A Workshop

Keck Center (Room 100) | 500 Fifth Street, NW, Washington, DC 20001

March 13, 2023, 2:00 pm - 5:00 pm ET

March 14, 2023, 9:30am - 4:00 pm ET

On the possible use of (multimodal) biomarkers to guide drug access and sustainability

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Apart from my Academic roles, in the past three years, I have provided scientific advices to: AbbVie, USA; Acadia, USA; BCG, Switzerland; Boehringer Ingelheim International GmbH, Germany; Compass Pathways, UK; EDRA-LSWR Publishing Company, Italy; Ferrer, Spain; Gedeon-Richter, Hungary; GLG-Institute, USA; Immunogen, USA; Inpeco SA, Switzerland; Johnson & Johnson USA; NeuroCog Trials, USA; Novartis-Gene Therapies, Switzerland; NetraMark, Canada*; Otsuka, USA; Pfizer Global, USA; PharmaMar, Spain; Relmada Therapeutics, USA*; Sanofi-Aventis-Genzyme, France and USA; Takeda, USA; Vifor, Switzerland; WCG-VeraSci/Clinical Endpoint Solutions, USA.

I do not bear any direct or indirect financial interest in products or concepts quoted in this talk.

These slides are both original or have been modified from my previous presentations. This slide deck in its flow is original and has never been presented before

*current

This file is updated to Feb 19th, 2023.

From Regulatory to Market Access for Innovative Medicines

Approved By FDA In Uncertainty

(and then reimbursed by who?)

Remarks by Commissioner Gottlieb to the Alliance for Regenerative Medicine's Annual Board Meeting

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Remarks by Scott Gottlieb, M.D.
Commissioner of Food and Drugs
Alliance for Regenerative Medicine's Annual Board Meeting
May 22, 2018
Washington, DC

" There is also the question of durability of response, which often can't be fully answered in any reasonably sized pre-market trial. For some of these products, there's going to be some uncertainty, even at the time of approval. "

https://www.fda.gov/NewsEvents/Speeches/ucm608445.htm

Table 1 ATMPs approved in Europe and/or the USA since 2015 [1, 31]

Brand and generic name	MA indication	MA date (EU)	MA date (USA)	Current status
Gene therapies				
Imlygic® Talimogene laherparepvec	Adults with regionally or distantly metastatic unresectable melanoma	12/2015	10/2015	EU: marketed US: marketed
Strimvelis® Autologous CD34+ cells transduced to express ADA	Patients with severe combined immunodeficiency due to adenosine deaminase deficiency	05/2016	-	EU: marketed
Kymriah® Tisagenlecleucel	Patients aged ≤25 years with B-cell ALL refractory, in relapse post-transplant or have had ≥2 relapses Adults with relapsed or refractory diffuse DLBCL after ≥2 lines of systemic therapy	09/2018	8/2017	EU: marketed US: marketed
Yescarta® Axicabtagene ciloleucel	Adults with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma, after ≥2 lines of systemic therapy	09/2018	10/2017	EU: marketed US: marketed
LUXTURNA® Voretigene neparvovec	Patients with vision loss due to inherited retinal dystrophy due to confirmed bialleleic RPE65 mutations and who have sufficient viable retinal cells	11/2018	12/2017	EU: marketed US: marketed
Zynteglo® Autologous CD34+ cells encoding βA-T87Q-globin gene	Patients aged ≥12 years with beta thalassemia who require regular blood transfusions	06/2019	-	EU: marketed
ZOLGENSMA® onasemnogene abeparvovec-xioi	Pediatric patients <2 years of age with spinal muscular atrophy with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene	-	05/2019	US: marketed
TECARTUS™ Brexucabtagene autoleucel	Adult patients with relapsed or refractory mantle cell lymphoma	-	07/2020	US: marketed
Cell therapies				
Zalmoxis® Allogeneic T cells genetically modified	Adults with high-risk hematological malignancies as an adjunctive treatment in HSCT	08/2016	-	EU: marketed
Alofisel® Darvadstrocel	Adult patients with complex perianal fistulas and non-active/mildly active luminal Crohn's disease, with no response to ≥1 conventional or biologic therapy	03/2018	-	EU: marketed
Tissue-based therapies				
MACI® Autologous cultured chondrocytes on porcine collagen membrane-specific marker protein	Adults with symptomatic cartilage defects of the knee	06/2013	05/2016	EU: withdrawn 09/2014 USA: marketed
Holoclar® Ex vivo expanded autologous human corneal epithelial cells	Adults with moderate to severe limbal stem cell deficiency, unilateral or bilateral, due to physical or chemical ocular burns	02/2015	-	EU: marketed
Spherox® Spheroids of human autologous matrix-associated chondrocytes	Adults with symptomatic articular cartilage defects of the femoral condyle and the patella of the knee	07/2017	-	EU: marketed

ADA adenosine deaminase, *ALL* acute lymphoblastic leukemia, *ATMPs* advanced therapy medicinal products, *DLBCL* diffuse large B-cell lymphoma, *HSCT* hematopoietic stem cell transplantation, *MA* marketing authorization

Pani L and Becker K., Clinical Drug Investigation, May 20, 2021 https://rdcu.be/ck1kH

The European point of contact between Regulators & Payers

Biomarkers in the context of the new EU HTA JCA Regulation?

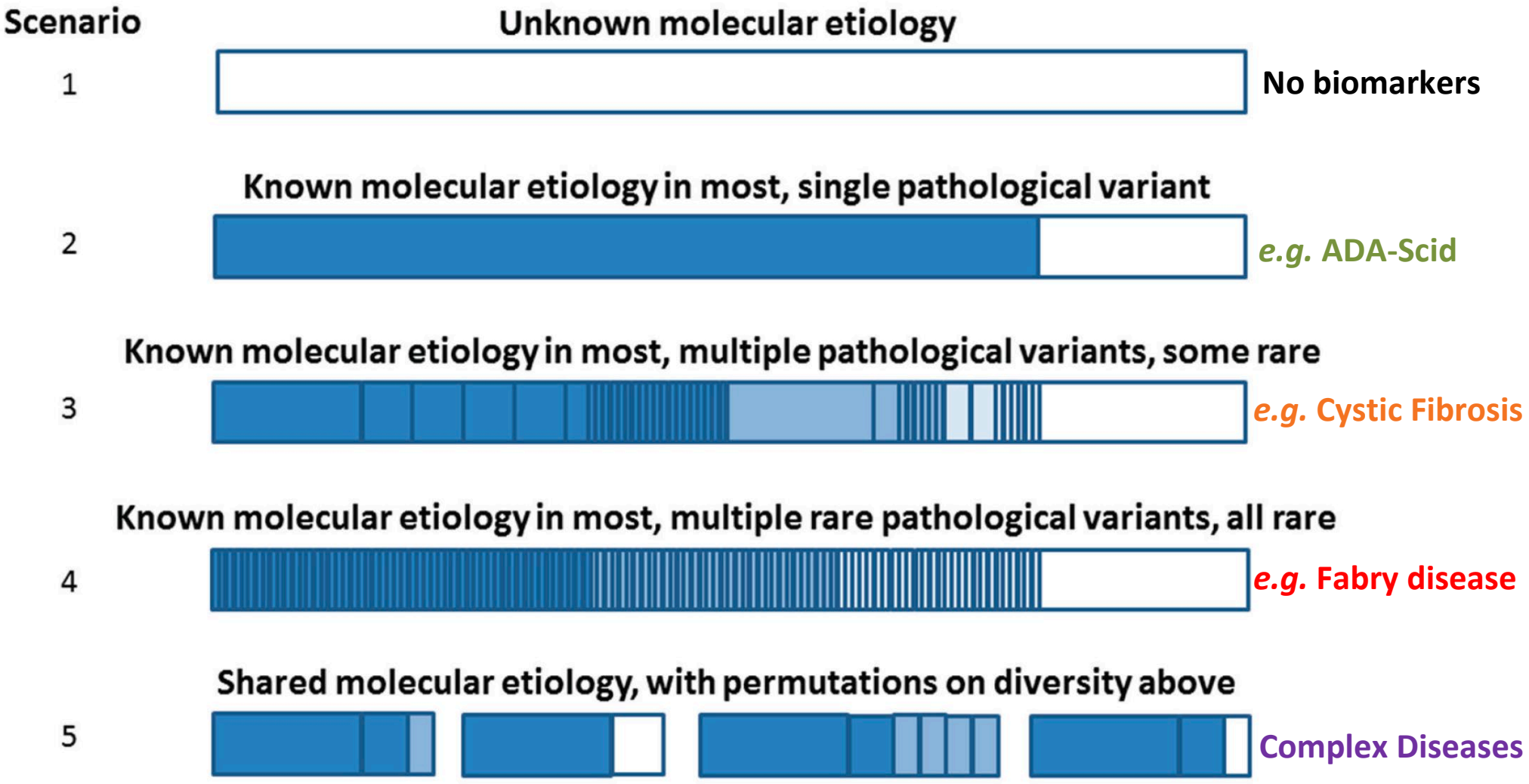
Objectives: The new Regulation (EU) 2021/2282 for EU Member States to adopt a non-binding but mandatory EU-wide Joint Clinical Assessment (JCA) is now in force. It aims to harmonise relative effectiveness assessment for pharmaceutical technologies and medical devices across the EU. The goal is for this EU JCA to replace the submission of multiple national dossiers.

Approach: JCA will be a descriptive summary of the clinical evidence of comparative effectiveness and safety for a given product, comprising of two distinct parts, one being a consolidated (not unanimous) HTA at the EU-level, and the other being national conclusions, including context specific further recommendations and country-specific requirements (*e.g.* different data requirement). Non-clinical evidence (*e.g.* health economic modelling of cost-effectiveness and budget impact) will not be assessed jointly but continue to be appraised nationally.

Timelines: Whilst the regulation came into force in January 2022, it will first be applied only in 2025 to oncology drugs and ATMPs, followed by orphan drugs in 2028 and finally all centrally approved remaining drugs and select medical devices in 2030.

https://www.eunethta.eu/jca/

Genetic biomarkers contribution to diseases

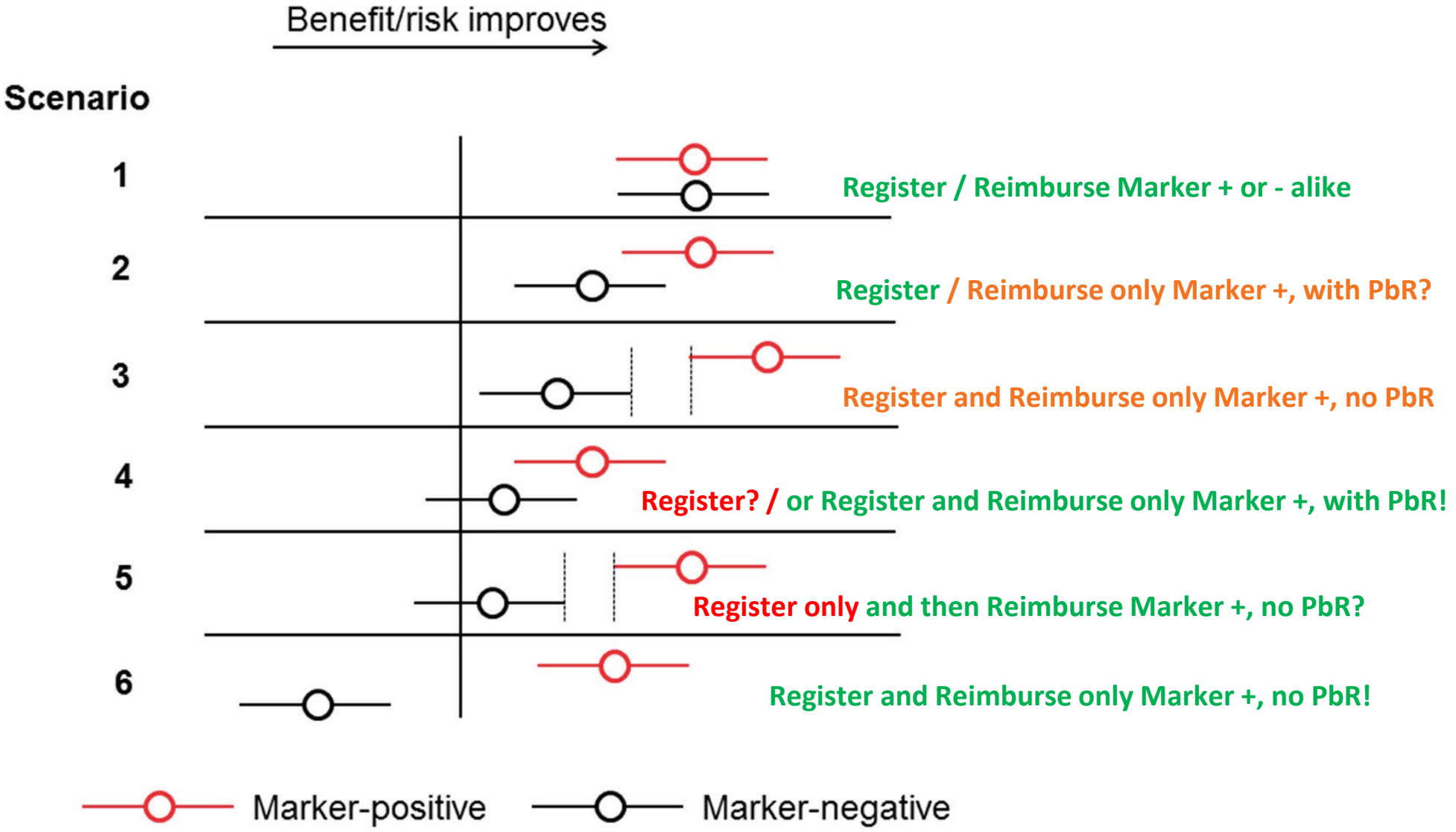


Modified from Michael Pacanowski, National Academies of Sciences, Engineering, and Medicine workshop presentation, March 8, 2017.

PbR = Payment by Results / AKA Pay for performance

https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/DFE38DB7329DA2553B4BED6F81C4F3F8FC12AB353A8A?noSaveAs=1 (accessed Feb 17, 2023)

Possible scientific and economic outcomes of biomarkers



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Can Biomarkers monitor long term value outcomes?

If a new pharma product breaks out of the marginal value mould of traditional pharmaceuticals with curative properties in indications with limited treatment options[1] we **need to have long term data**

Assuming that the effects are at least long term, if not curative, has two key implications:

I. Show that long lasting curative effects are likely to **reduce avoidable costs** of patient support and managing chronic (co)morbidities[2].

II. Show even more that early cures or **substantial benefits at younger ages** could help produce significant gains in work productivity for patients compared to treatments that bring marginal gains over many years.

[1]Modified from [1]Bubela et al., 2016; [2]Abou-El-Enein et al., 2016

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